REMARKS

I. Status of the Claims and Claim Amendments

Claims 60, 66-71, and 73-104 are currently pending. Applicants thank the Examiner for entering the Request for Continued Examination filed on August 2, 2003, and for entering claims 97-104, presented in that paper.

Applicants now amend claim 68, solely to clarify its relationship to claim 67, as discussed below. That amendment does not change the scope of any of the pending claims and does not introduce new matter. Instead, it merely re-phrases the claim language to clarify that the "cow, pig, rabbit, or mouse" is one that is capable of producing milk, for example, a female of the species. Applicants also re-phrase claim 69 to follow the structure of claim 68 more closely. Similarly, that amendment merely re-phrases the claim, introduces no new matter, and does not change the scope of the pending claims.

Applicants also amend claims 97-104 to change the phrase "overexpressed recombinant intimin" to simply "recombinant intimin," as discussed below. This change does not present new matter and does not limit the scope of the pending claims. Support for this amendment may be found throughout the application as a whole, for example, in working examples I-III at pages 21-38. That support is discussed more fully in the following section of these remarks.

Applicants respectfully request the entry of these amendments.

II. Claims 60, 66-71 and 73-104 Do Not Contain New Matter

The Office contends that the phrase "overexpressed recombinant intimin" in claims 97-104 is not supported by the application as filed according to 35 U.S.C. § 112,

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first paragraph, and that introduction of this phrase constitutes new matter. (Office Action at pages 2-3, paragraph 5.) The Office correctly notes that the instant application does describe making intimin recombinantly. (Office Action at page 3, stating that "[n]ormal induction of expression of the recombinantly produced intimin was found.") However the Office contends that support for recombinantly produced intimin does not go beyond histidine-tagged intimin. (*Id.*) Applicants traverse this rejection, but have amended the phrase to recite simply "recombinant intimin," in order to speed prosecution.

The Office also asserts that the phrase "enriched or purified intimin" is not supported throughout its scope according to 35 U.S.C. § 112, first paragraph. The Office asserts that expression with a histidine tag is the only method described for making "enriched intimin." (Office Action at pages 3-5, paragraph 6.) Applicants also traverse this rejection.

Literal support for the claim terminology is not necessary to satisfy the requirements of 35 U.S.C. § 112, first paragraph. M.P.E.P. § 2163(I)(B). Instead, newly added limitations or amendments may be supported implicitly or inherently, as well as by express terminology. *Id.* Further, written description support, by any of these means, is considered from the point of view of one of ordinary skill in the art. M.P.E.P. § 2163.01(I).

The Office essentially asserts that the "overexpressed recombinant intimin" or "enriched intimin" should be limited to "histidine-tagged intimin" because the intimin prepared in Examples II and III was histidine-tagged. However, the application as a whole points out that histidine tagging is merely one aspect of the instant invention.

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For example, the Office asserts that the definition of "enriched intimin" is found at page 7, first paragraph, of the instant application. The Office asserts that "enriched intimin" is "defined through a narrative, which teaches the step of 'expressing a protein comprising intimin having a histidine tag,' followed by the step of 'enriching the intimin.'" Yet, that paragraph is not structured to imply that histidine tagging is the only way to make "enriched intimin" in the context of the instant invention. Instead, it first states that "[t]he present invention relates to an enriched protein comprising intimin or a portion of intimin that retains wild-type binding activity or that induces antibodies that block wild-type binding activity." Then it states that "[t]he invention ***also*** relates to a protein, comprising intimin . . . having a histidine tag." (*Id.*, emphasis added.) The use of the word "also" clearly indicates that histidine tagging is not meant to be the exclusive method of making intimin for administration.

Indeed, patents that are related as having an overlapping inventive entity and as claiming priority to the same U.S. provisional applications illustrate methods of enriching intimin both with and without a histidine tag. For example, see claims 1 and 2 of U.S. Patent Nos. 6,261,561 and 6,406,885. (Submitted herewith in the Information Disclosure Statement.) These also show that the instant inventors' approach was not meant to be drawn exclusively to histidine-tagged proteins.

Other parts of the instant application also clarify that histidine tagging was not meant to be the exclusive method of making "enriched intimin" or "recombinant intimin." For example, the first sentence of the "Detailed Description" section of the application at page 11 points out that the application is directed to "an enriched protein comprising intimin" and "a purified protein comprising intimin." The next sentence points out that

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the application is "*also directed to*" a protein with a histidine tag. (Emphasis added.) If histidine tagging was the only intended method of making the enriched or purified intimin, including the word "also" would not make logical sense. That language demonstrates that "enriching and purifying," such as by recombinant expression, is one aspect of the invention, while use of a histidine tag is a different aspect of the invention. In other words, histidine tagging is one method of making "enriched intimin" or "recombinant intimin," but it is not the only method.

Similarly, the middle paragraph of page 13 points out that the instant application relates to "a method of promoting a protective immune response." In that method, the application points out that "preferably the intimin . . . is purified or enriched." The application states in a later sentence that "it is also *preferred* that the intimin . . . has a histidine tag." (Emphasis added.) Again, it is clear from those sentences that the histidine tag is one way of making an enriched or purified intimin protein according to this invention, but it is not the only way to do so. If it was the only way, the comment that the histidine tag is "preferred" would not make logical sense. The final paragraph on page 13 and the first paragraph on page 14 follow a similar pattern.

Original claims 15-18, 19-22, and 23-26 provide another illustration. In those claims, reciting methods of administering intimin or antigens, the histidine tag element appears only in a dependent claim, and in a separate claim from either the "enriched" or "purified" intimin. (Specification at pages 88-89.)

In summary, many parts of the application show that histidine tagging is one method of making the instant "enriched or purified intimin," but it is not the only method of making it.

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Applicants also respectfully point out that the Office's current definition of "enriched intimin" is very different from the definition it used throughout the previous two years of prosecution of this application, despite relying upon the same sentences at the top of page 7 as the source of that definition. (Compare, for example, Office Action of August 15, 2001, at page 4, paragraph 5, and Office Action of April 22, 2003, at page 5, paragraph 9.) Previously the Office found "enriched intimin" so broadly defined as to cover intimin produced during natural disease. (*Id.*) Now, the Office finds "enriched intimin" so narrow as to cover only Applicants' working examples. Applicants respectfully submit that neither of these positions presents the "broadest reasonable interpretation" of the instant claim language. See M.P.E.P. § 2163(II)(A)(1).

The Office also contends that "enriched intimin" is not supported in the context of "administering" an intimin. (Office Action at page 4, lines 5-9.) Yet, those sections of the application detailed above also provide clear support for "administering" an "enriched intimin." See for example, the middle paragraph at page 13, describing obtaining a protective immune response in a patient by "administering to a patient intimin," then stating that "[p]referably the intimin . . . is purified or enriched." These sentences clearly link "administering" to the "enriched intimin." A separate sentence in that paragraph states that a histidine tag would also be "*preferred*." (*Id.*, emphasis added.) If the only contemplated method of making the "enriched intimin" was to use a histidine tag, it would not make sense to call that method "preferred." Again, claims 15-18 follow a similar pattern in the context of administering intimin.

For all of these reasons, "recombinant intimin" and "enriched intimin" are fully supported by the application, and Applicants request the withdrawal of these rejections.

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III. Claim 68 Is Definite

The Office contends that claim 68, which depends from claim 67, is broader in scope than claim 67. (Office Action at page 5.) Applicants traverse this rejection, but, merely to speed prosecution, offer a clarifying amendment.

Claim 67 is directed to a "cow, pig, rabbit and mouse," while claim 68, prior to amendment, recited a "milk-producing animal." Applicants note that, because of the relationship between those two claims, one of ordinary skill in the art would recognize that the animal in claim 68 is a "milk-producing" member of one of the four species listed in claim 67 (e.g., a mature female).

Applicants' amend claim 68 to replace the phrase "wherein the host animal is a milk-producing animal" with "wherein the cow, pig, rabbit, and mouse is milk producing." The amendment is simply intended to further clarify the relationship between claims 67 and 68. It does not change the scope of the pending claims.

In light of these remarks and the claim amendments, Applicants respectfully request the withdrawal of this rejection.

IV. Claims 60, 66-67, 83-84, 89, and 97 Are Nonobvious over Dougan

The Office has withdrawn a previous rejection of the instant claims over a combination of Dougan et al. (U.S. Patent No. 5,747,293; "Dougan") and another publication, yet issues a new rejection of claims 60, 66-67, 83-84, 89, and 97 over Dougan alone. Applicants traverse this rejection for the same reasons Applicants have traversed other rejections involving Dougan throughout the prosecution of this application.

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This rejection is not a *prima facie* case of obviousness. First, there is no motivation or desire for one of ordinary skill in the art to modify the teachings of Dougan. Second, if one of ordinary skill in the art were, nevertheless, to modify them, that modification would not include all of the elements of Applicants' claims. Third, Dougan's teachings provide no reasonable expectation of success in performing Applicants' claimed methods.

A. There is No Motivation to Modify Dougan

The Office contends that Dougan teaches all of the elements of claims 60, 66-67, 83-84, 89, and 97. (Office Action at pages 5-7.) Yet, Applicants respectfully reiterate that this rejection is not based upon the teachings of Dougan as a whole, and therefore, traverse this rejection.

Dougan provides absolutely no discussion of how to administer antibodies, treat EHEC infection, or provide immunoprotection for potential EHEC sufferers. Instead, Dougan's disclosure is focused almost exclusively on making anti-intimin antibodies and using them ***in vitro***, to detect EPEC or EHEC cells in samples. (Dougan at Abstract; col. 1, lines 3-8; col. 3, line 48, to col. 4, line 42; Examples 1-4.) The Office's contention that Dougan teaches or provides guidance for administering intimin for therapeutic purposes comes from a single comment in Dougan stating that antibodies that recognize EPEC intimin but do not recognize EHEC intimin "will therefore be useful in both the detection and/or treatment of EPEC infection." (Dougan at col. 2, lines 41-44.) The phrase "and/or treatment" is the only reference in Dougan to anything beyond *in vitro* use of its antibodies.

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This phrase cannot bear up to the weight the Office gives it. First, Dougan's antibodies actually recognize the EPEC strain of *E. coli*. In contrast, the claims here require antibodies that block the binding of the EHEC strain to mammalian cells. Antibodies that recognize EPEC intimin but do not recognize EHEC intimin simply cannot be used in Applicants' methods.

Second, Dougan's statement that its antibodies "will therefore be useful in both the detection and/or treatment of EPEC infection" lacks supporting data. Its working examples describe only making the antibodies using the standard rabbit inoculation and mouse hybridoma techniques, and using them *in vitro* to detect EPEC cells in culture. (Dougan at Examples 1-4.) Dougan provides absolutely no data suggesting that those antibodies could block binding of EPEC to mammalian cells, let alone that they could provide passive immune protection as Applicants claim.

Perhaps aware of Dougan's deficiencies, the Office now attempts support its contentions with other locations in Dougan beyond the phrase discussed above, such as col. 1, lines 48-51, col. 2, lines 52-56 and col. 3, lines 20-42. But the Office reads meaning into those sections that their text does not support. The first section describes merely the general function of the intimin protein during disease, the second provides Dougan's definition of "antibody," as being monoclonal or polyclonal, and the third discusses the section of the intimin protein that Dougan's antibodies recognize. Given that these sections do not relate to any method of administering antibodies for a treatment, the Office could only have cited them by impermissible hindsight from Applicants' specification.

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For these myriad reasons, Dougan cannot motivate one of ordinary skill in the art to administer enriched or purified intimin as Applicants claim. This alone shows that the instant rejection is not a *prima facie* case of obviousness. Yet Dougan fails the other elements of the obviousness inquiry as well.

B. Dougan Does Not Teach or Suggest All of the Elements of Applicants' Claims

Dougan also fails to teach or suggest antibodies that "block binding of enterohemorrhagic *E. coli* to a mammalian cell," as required in all of Applicants' claims. Dougan does note that the approximately 280-amino acid carboxy-terminal region of EPEC and EHEC intimin is suitable for "use in detection." (Dougan at col. 1, lines 3-8; col. 3, line 48, to col. 4, line 42; Abstract.) While it is correct that this part of intimin is involved in mammalian cell recognition, Dougan's disclosure indicates that the 280-amino acid carboxy-terminal region of intimin was chosen as an antibody target merely because this is the part of the intimin protein that is found on the outside of the cell, and so is easiest to access. (Dougan at col. 2, lines 6-24.) Thus, Dougan and co-inventors did not intend to make antibodies that can block binding of EPEC intimin to mammalian cells, let alone EHEC intimin to mammalian cells. (Office Action at page 6, second complete paragraph.)

Further, Dougan itself provides evidence suggesting its antibodies *cannot* block binding of intimin to mammalian cells. Not all antibodies that bind to the 280 amino-acid carboxy-terminal portion of intimin are expected to block binding of bacteria to mammalian cells because only the final 192 amino-acids of that region are actually implicated in mammalian cell adherence. (See Dougan at col. 2, lines 6-7.) In fact,

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Dougan's antibodies did not recognize the final 149 amino acids of the EPEC intimin protein, suggesting that they cannot block binding of EPEC to cells. (Dougan at col. 6, line 49, to col. 7, line 1.) This suggests that Dougan's antibodies could not be used in Applicant's invention, not only because they recognize EPEC and not EHEC intimin, but also because they cannot block binding to mammalian cells. Yet, antibodies that block binding of EHEC to mammalian cells is a specifically-recited element of all of Applicants' claims.

C. There is No Reasonable Expectation of Success in Modifying Dougan

Finally, there is also no reasonable expectation of success. Again, Dougan simply asserts, without any supporting discussion or data, that antibodies that recognize EPEC intimin but do not recognize EHEC intimin "will therefore be useful in both the detection and/or treatment of EPEC infection." (Dougan at col. 2, lines 41-44.)

First, as previously explained, EPEC and EHEC are not the same, and the claims here require antibodies that block the binding of EHEC to mammalian cells. Second, all of Dougan's working examples relate merely to using anti-intimin antibodies *in vitro* to detect EPEC in samples. Third, as discussed above, Dougan's anti-EPEC intimin antibody does not bind to the final 149 amino acids of intimin, which constitute the majority of the cellular binding region of EPEC intimin. Thus, there is no indication that Dougan's EPEC-specific antibodies would actually block binding of EPEC to mammalian cells, let alone block binding of EHEC to mammalian cells.

Finally, nothing in Dougan suggests that, if one were actually to administer enriched or purified intimin to an animal, the anti-intimin antibodies would provide any

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degree of immune protection. Dougan presents no data showing that its antibodies could be used in any treatment protocol, let alone in one that provides passive immune protection to a patient.

Given these deficiencies, Applicants conclude that the Office improperly bases this rejection, by hindsight, on Applicants' disclosure. *See, e.g., In re Dow Chem. Co. v. American Cyanamid Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531-2 (Fed. Cir. 1988). It appears to Applicants that the Office has picked and chosen only so much of Dougan as would support this rejection without considering that Dougan as a whole is focused upon using antibodies for detection and provides no explanation of how any anti-intimin antibodies could be used successfully in any treatment protocol. *See In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965). Therefore, the Office has not met any of the three prongs of a *prima facie* case of obviousness, and Applicants respectfully request the withdrawal of this rejection.

D. Applicants Methods Have Shown Unexpected Results and Achieved Commercial Success

As fully developed above, the Office has not made out a *prima facie* case of obviousness. For this reason alone, Applicants submit that all of the pending claims are allowable. Nonetheless, to facilitate prosecution, and not in acquiescence to the presentation of a *primia facie* case, Applicants previously provided information and data supporting "objective indicia" of nonobviousness.

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i. Unexpected Results: The Dean-Nystrom Abstract

Applicants previously presented to the Office an abstract from Dean-Nystrom et al. as evidence of unexpected results. The Preliminary Amendment of May 24, 2001, at pages 9-10, describes the Dean-Nystrom experiment in detail.

In Dean-Nystrom's experiment, a group of pregnant sows were vaccinated twice with a purified EHEC intimin protein. This resulted in a change in the colostral titers of anti-intimin antibodies from a base-line of ≤ 100 to ≥ 100,000. Their piglets were challenged with a strain of EHEC after suckling for up to eight hours. Another group of pregnant sows were not vaccinated, and their piglets were challenged as controls, again, after up to eight hours of suckling. Nearly all of the 27 control piglets showed A/E bacteria in the large intestine and ≥ 10^6 CFU of inoculum bacteria per gram of cecal tissue. In contrast, only 5 of the 22 piglets whose mothers had been given intimin showed either A/E bacteria or ≥ 10^6 CFU/g. Thus, these results demonstrate successful passive immune protection, in which patients were protected from challenge with EHEC bacteria.

The Office previously asserted that the results presented in the Dean-Nystrom abstract are not commensurate in scope with the invention as claimed. First, the Office asserted that the results are limited to pigs. (See the August 15, 2001, Office Action, at page 8.) Applicants previously acknowledged that the hosts and patients of Applicants' claims comprise several animals, including humans. (Amendment filed January 29, 2002, at pages 8-9.) However, the pig model was chosen for the Dean-Nystrom experiment largely because the pig immune system it is a *good and accepted model* in the art for the human immune system, among others. (*Id.*; *see also* Applicants remarks

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filed January 29, 2002, at pages 8-9, and the exhibit attached thereto.) Applicants cannot ethically perform experiments like those of Dean-Nystrom on humans, and such experiments are barred by Food and Drug Administration regulations.

In addition, the Federal Circuit has repeatedly maintained that a showing of unexpected results for a species in a claimed genus is sufficient to rebut a *prima facie* case of obviousness throughout the entire scope of the claim when one skilled in the art can reasonably conclude that similar results would be obtained for other members of the genus. *See, e.g., In re Chupp*, 816 F.2d 643, 646, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987); *In re Clemens*, 622 F.2d 1029, 1036, 206 U.S.P.Q. 289, 296 (CCPA 1980). These holdings are particularly relevant here, as the pig is a commonly used model of other immune systems such as that of humans. (Amendment filed January 29, 2002, at pages 8-9, and exhibit attached thereto.)

Second, the Office contended that the Dean-Nystrom abstract is not applicable to non-colostral antibodies with titers lower than 100,000. (Office Action of August 15, 2001, at page 8.) However, Applicants previously pointed out that it would be difficult to test different sources and titers because this experiment relies on the natural physiological responses of the sows to the vaccine. (Amendment filed January 29, 2002, at pages 8-9, and exhibit attached thereto.)

In summary, Office has not provided credible factual evidence according to the standards of *Zurko* and *Lee* to support its contentions about the Dean-Nystrom abstract. Instead, the Office Action of August 15, 2001, merely asserted that the abstract recites antibodies from colostrum in a particular titer and asserts that the instant claims are not

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limited to colostral administration or a to particular titer. (See the Office Action of August 15, 2001, at page 8, and the Office Action of October 4, 2002, at pages 6-7.)

ii. Commercial Success: Licensing of the Invention

In the Preliminary Amendment filed May 24, 2001, Applicants also provided evidence of commercial success, through a license by Biosynexus Incorporated. This licensee has licensed the instant invention merely from the strength of the disclosure and the underlying research, and prior to the issuance of any claim. Thus, by definition, this license is commensurate with the scope of the claims as a whole.

It is well known that the commercialization of biotechnology methods and products is often exceedingly long and requires the approval of one or more regulatory agencies. The instant license demonstrates commercial success on its face because the licensee has recognized with its pocketbook the value of the disclosed technology at an early stage and will absorb much of the very high costs associated with commercial development and regulatory approval of the method. Indeed, the purpose of a license is to bring the subject of an invention to market. Thus, by definition, the license of a claimed technology at the stage of development of the claimed technology is the very essence of commercial success of a product.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not found herewith to Deposit Account 06-0916.

Respectfully submitted,

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Dated: January 30, 2004

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